Effect of a Pharmacist on Adverse Drug Events and Medication Errors in Outpatients With Cardiovascular Disease

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Background: Adverse drug events and medication errors are threats to quality care. Inpatient studies suggest that a pharmacist may reduce these events, but outpatient studies have not been forthcoming.

Methods: We conducted a pooled analysis of 2 randomized controlled trials to determine the effect of pharmacist intervention on adverse drug events and medication errors. We studied 800 outpatient cases of hypertension stratified into complicated (n=535) and uncomplicated (n=265). Patients in the complicated stratum had heart failure or other cardiovascular complication. Computer programs examined 1-year electronic record data to identify events classified as adverse drug events and preventable or potential adverse drug events. Medication errors included preventable and potential adverse drug events.

Results: Of the 800 participants (mean [SD] age, 59 [10] years), 484 (90.5%) and 258 (97.4%) participants remained in the complicated and uncomplicated strata, respectively, at 12 months. Compared with the control group, the risk of any event was 34% lower in the intervention group (risk ratio, 0.66; 95% confidence interval [CI], 0.50-0.88), including a lower risk of adverse drug events (risk ratio, 0.65; 95% CI, 0.47-0.90), preventable adverse drug events (risk ratio, 0.52; 95% CI, 0.25-1.09), potential adverse drug events (risk ratio, 0.70; 95% CI, 0.40-1.22), and medication errors (risk ratio, 0.63; 95% CI, 0.40-0.98).

Conclusions: This post hoc analysis suggests that pharmacist intervention to improve medication use in outpatients with cardiovascular disease decreases the risk of adverse drug events and medication errors. Further studies are needed to confirm this finding.

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ADVERSE DRUG EVENTS (ADEs) and medication errors (MEs) are common and costly threats to the quality of care. Such drug-related problems are common in outpatients in the United States and added together with other drug-related problems

See also pages 737, 740, and 750

cost $77 to $177 billion annually.[1,2] While the incidence of these events among inpatients is well characterized, such events often go unnoticed in the outpatient setting and are more difficult to measure.[3] From 20% to 28% of these ADEs are preventable because they derive from an error.[4,5] However, accurate estimates of the numbers and costs of MEs in outpatient settings have not been forthcoming.[6] Studies estimate that they occur in 2% to 21%

of outpatient prescriptions[7-9] (depending on how *error* is defined and the measurement setting) and result in ADEs that are largely preventable.[4,5,8,10] Such preventable ADEs in Medicare recipients cost the US an estimated $887 million.[11] Patients with more complicated drug regimens, such as those with cardiovascular disease, are particularly at risk.[5,10,12]

A potentially untapped resource to prevent ADEs and MEs is the pharmacist. Pharmacists are particularly well positioned to provide the necessary medication instruction to patients,[13,14] which is an overarching recommendation of the Institute of Medicine's Committee on Identifying and Preventing Medication Errors.[6] Pharmacists may also provide drug monitoring and corresponding feedback to assist physicians in prescribing decision making and laboratory monitoring. Studies in inpatient settings have demonstrated favorable effects of pharmacists in reducing ADEs and MEs.[15-17] However, few

interventions have tested the effect of pharmacists on incident events in outpatients. We therefore determined the effect of pharmacist intervention on incident ADEs and MEs in outpatients with heart failure or hypertension receiving care in a city-county health care system.

Data were pooled from 2 randomized controlled trials, one trial of patients with heart failure[14,18] and the other trial of patients with hypertension.[19] The trials had similar designs and were conducted in the same health care setting with the same primary objective: to test the effect of pharmacist intervention on medication adherence and relevant health outcomes. Assessment of ADEs and MEs were secondary study objectives. Details of the original studies have been previously described.[14,18,19] The studies were approved by the institutional review boards of Indiana University–Purdue University at Indianapolis, Indiana, and the University of North Carolina at Chapel Hill.

STUDY SETTING AND PARTICIPANTS

Participants for both trials were recruited at the outpatient practices of Wishard Health Services, Indianapolis, Indiana. Wishard is located on the campus of Indiana University School of Medicine at Indianapolis and is part of a city-county teaching hospital serving the socioeconomically disadvantaged and medically vulnerable population of Marion County, Indiana. Adult outpatients who receive care at Wishard Health Services are predominately women (66%) with a mean (SD) age of 57 (15) years. Most patients receive their prescription medications through state and local assistance plans at no cost.

Patients were eligible for the heart failure study if they had a diagnosis of heart failure confirmed by their primary care physician, were 50 years or older, and regularly used at least 1 cardiovascular medication for heart failure. Patients were eligible for the hypertension study if they had a diagnosis of hypertension, were at least age 18 years, and were taking at least 1 antihypertensive drug. Participation in either study required that the patient planned to receive all primary care at the study center and their prescription drugs at a Wishard pharmacy. The heart failure study was conducted from February 2001 to November 2004, and the hypertension study was conducted from January 2002 to May 2005.

A comprehensive medication history and medication assessment was conducted by pharmacists at baseline. A research assistant then randomly assigned patients to either an intervention or control group using a computer randomization protocol. In the heart failure study, there were 314 participants (122 in the intervention group and 192 in the control group). In the hypertension study, there were 492 participants (246 in the intervention group and 246 in the control group) of whom 6 had incomplete ADE and ME data and were excluded from this analysis. Participants in the hypertension study were stratified into complicated and uncomplicated strata prior to randomization. Participants were considered to have complicated hypertension if they had prior evidence of a vascular disorder or insult indicating poorly controlled hypertension, including myocardial infarction, coronary heart disease, stroke, heart failure, or renal insufficiency. We ascertained these complications using diagnostic, procedural, radiologic, and laboratory data from the Regenstrief Medical Records System.[20,21] Patients with uncomplicated hypertension had no history of cardiovascular complications from their disease. We combined participants from the heart failure study with the participants in the complicated stratum of the hypertension study to form a larger group of patients with complicated hypertension. Thus, the combined studies of 800 participants formed 2 strata of complicated (232 intervention and 303 control group patients) and uncomplicated (134 intervention and 131 control group patients) hypertension.

INTERVENTION

The intervention was provided by specifically trained and equipped pharmacists who communicated regularly with intervention participants to dispense medications and provide them with ongoing oral and written instruction. Following the baseline medication history, participants were provided medications in containers that enabled electronic monitoring of adherence to the prescribed cardiovascular medications and medication information designed for persons with low health literacy. The intervention pharmacist used a study computer that was integrated into the electronic medical record system for the purpose of monitoring prescription and nonprescription medications, tracking materials provided to patients, and documenting communications with patients, nurses, and physicians. The intervention was similar in both studies except for its duration and follow-up. In the heart failure study, intervention participants received the intervention for 9 months with a 3-month postintervention follow-up period. In the hypertension study, the intervention lasted for 12 months with a 6-month postintervention follow-up.

CONTROL

Participants assigned to the control arm were observed for 12 and 18 months in the heart failure and hypertension studies, respectively. Participants in the control group received usual care at the same pharmacy from nonintervention pharmacists who did not have access to the study computer, instructional materials, or the study computer monitoring program. Pharmacists serving control participants had similar access to health system physicians and nurses.

MEASUREMENTS

Data on ADEs and MEs were collected for 12 months using a program developed for a separate study.[22,23] This program examined coded and text electronic health record data to identify triggers suggestive of selected ADEs and MEs in outpatients. A list of triggers was drawn up a priori and included more than 100 ADEs or MEs commonly observed in adult general practices (**Table 1**). Examples of relevant events included angiotensin-converting enzyme (ACE) inhibitor–related allergy or cough, toxic serum digoxin concentrations, or use of nonsteroidal anti-inflammatory drugs in persons with elevated serum potassium concentrations or renal insufficiency. Computer programs identified triggers by comparing with coded (laboratory and prescription records) and text data (transcribed and dictated physician notes). Coded data were available for both studies; however, we had access to text data only for the heart failure study. Computer programs were run by programmers blinded to treatment group assignment after patients had completed their full participation in the trials. A trained nurse abstractor, also blinded to group assignment, verified whether an ADE or ME had actually occurred using both electronic health records and the paper medical records. The nurse adjudicator was trained using methods similar to those used in previous studies that had good interrater agreement (κ values of 0.81[5] and 0.89[4]) and had more than 15 years of experience in quality assurance including medication safety research.

OUTCOMES

Events were classified by the nurse as ADEs, preventable ADEs, and potential ADEs as defined by Bates et al[24]: ADEs were defined as drug events that produced harm; preventable ADEs were drug events that produced harm and were considered to have been the result of a medication error; and potential ADEs were medication errors that had the potential for harm but no evidence of harm was observed or the error was intercepted before reaching the patient (such as a prescription for a drug to which the patient was reportedly allergic). Our criteria for potential ADEs were similar to those described by Poon and colleagues[25] for an inpatient study. Medication errors were mistakes made in prescribing or drug monitoring. For the purpose of this study, MEs were the sum of preventable and potential ADEs.

INDEPENDENT VARIABLES

Data on age, sex, race, years of formal education, marital status, household income adequacy, and insurance were collected at the baseline interview. We categorized perceived income adequacy as "comfortable," "just enough to get by," or "not enough to get by."[26,27] Insurance included Medicare, Medicaid, Health Advantage (a medical assistance program available to low-income patients), private, or none. Encounters were any visit made to the health system requiring registration. Comorbidities included any chronic disorder for which a medication would likely be prescribed.

STATISTICAL ANALYSIS

Comparisons of patient characteristics between the intervention and control groups, stratified by complication status, were made using t tests for continuous variables and χ^2 tests for categorical variables with a P value less than .05 considered statistically significant. The χ^2 or Fisher exact tests were also used to test the hypotheses that the ADEs and MEs among participants were independent of intervention or control group assignment. We calculated the overall and specific distribution of ADEs, preventable ADEs, potential ADEs, and MEs experienced by patients in complicated and uncomplicated strata for 12 months. Medication errors were the subset of ADE events involving MEs; namely, preventable ADEs and potential ADEs. Risk ratios for the counts of ADEs or MEs were calculated for intervention and control participants using Poisson regression models.

RESULTS

The **Figure** is the study participant flowchart. A total of 800 participants with cardiovascular disorders were studied, 314 from the heart failure study and 486 from the hypertension study. These participants formed groups of complicated (n=535) and uncomplicated hypertension (n=265) disease for pooled analysis. Considering persons lost to follow-up and deaths at 12 months, 484 (90.5%) and 258 (97.4%) participants remained in the complicated and uncomplicated strata, respectively. Study participants were a mean (SD) of 59 (10) years old; 71.1% were women; and 60.4% were African American (**Table 2**). Participant balance on important background characteristics between control and intervention groups was good. Counts of prescription medications at 12 months were similar to baseline counts for complicated (*P*=.57) and uncomplicated (*P*=.74) strata; counts of prescribed cardiovascular-specific medi-

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Table 1. Examples of Adverse Drug Event and Medication Error Trigger Types

Potassium
Hypokalemia, serum potassium <3 mEq/L
Hyperkalemia, serum potassium >5.5 mEq/L
Potassium-sparing diuretic and hyperkalemia
Thiazide diuretic and hypokalemia
ACE inhibitor and hyperkalemia
Sodium polystyrene sulfonate

Liver/Kidney
Elevated liver enzyme levels
Acetaminophen >4100 mg/d
Statin and elevated ALT (>70 U/L)
Statin and muscle pain
Renal insufficiency
NSAIDs and increased serum creatinine level
Calcium channel blocker and edema
Ketorolac for >5 d

Glucose/Diabetes
Metformin toxic effects
Glucocorticoid-associated glucose intolerance
Hypoglycemia, blood glucose level <54 mg/dL

Drug Interaction
Drug-drug interaction
NSAIDs and gastritis
Drugs to avoid in the elderly
Use of 2 or more acetaminophen medications

Cardiovascular
ACE inhibitor allergy
ARB prescribed to replace ACE inhibitor
Digoxin >1.7 ng/mL
Antihypertensive drug and dizziness
Nitrates and hypotension
β-Blocker and bradycardia
Risk of drug-induced QTc interval prolongation

Anticonvulsants
Carbamazepine concentration not measured
Dizziness
Phenytoin and nystagmus

Infection/Antimicrobials
Oral candidiasis
Vaginal candidiasis
Oral metronidazole or vancomycin
Topical steroid for rash
Urticaria
Clostridium difficile colitis

Respiratory
Theophylline >20 µg/mL
β-Blocker and asthma

Other
Thyroxine toxic effects
Evidence of bleeding

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

SI conversion factors: To convert potassium to millimoles per liter, multiply by 1.0; ALT to microkatals per liter, multiply by 0.0167; glucose to millimoles per liter, multiply by 0.0555; digoxin to nanomoles per liter, multiply by 1.281.

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cations at 12 months were also similar to baseline for complicated (*P*=.53) and uncomplicated (*P*=.48) strata.

EVENT IDENTIFICATION AND VERIFICATION

The computer monitor identified 1029 triggers that were further analyzed for evidence of ADEs and MEs. Of the 1029 triggers, 694 (67.4%) occurred in the control group, and 335 (32.6%) occurred in the intervention group. After further analysis by the nurse adjudicator, of the 694 triggers in the control group, 135 ADE or ME events were verified (positive predictive values, 19.5% and 10.0% for coded and text data, respectively), and the 335 triggers in the intervention group yielded 75 ADE or ME events (positive predictive value, 22.4%).

Of the 210 events, the 5 most common, occurring in a total of 68 participants, included receipt of a prescription for a drug that should be avoided in elderly patients
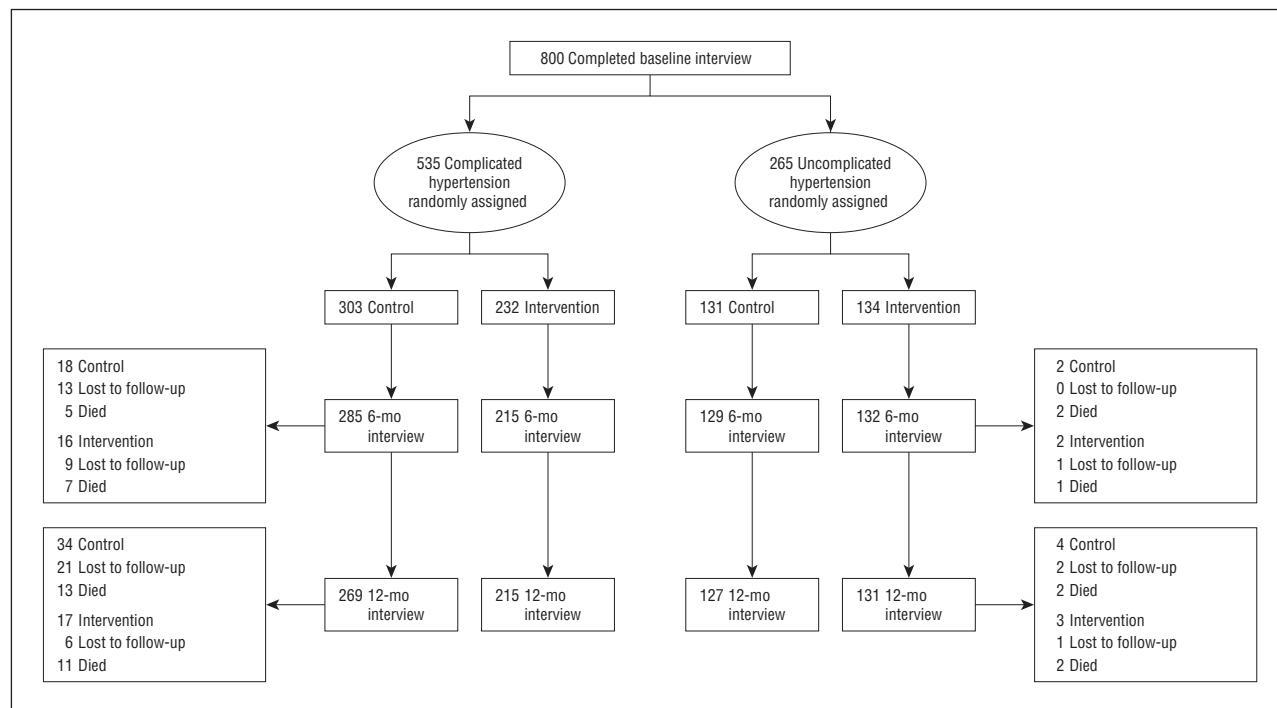
Figure. Study participant flowchart.

Table 2. Patient Characteristics Stratified by Complication and Intervention[a]

Characteristic	Complicated (n=535)			Uncomplicated (n=265)		
	Control (n=303)	Intervention (n=232)	P Value	Control (n=131)	Intervention (n=134)	P Value
Age, mean (SD), y	62 (9.9)	61 (9.3)	.89	54 (10.3)	54 (10.0)	.84
Education, mean (SD), y	11 (2.6)	11 (2.5)	.27	12 (2.2)	12 (2.5)	.89
Women, No. (%)	207 (68)	167 (72)	.36	98 (75)	97 (72)	.65
African American, No. (%)	168 (55)	132 (57)	.74	91 (69)	92 (69)	.89
Insufficient household income, No. (%)	119 (39)	88 (38)	.75	60 (46)	62 (46)	.94
Married, No. (%)	75 (25)	61 (26)	.69	34 (26)	25 (19)	.15
Medicare, No. (%)	160 (53)	118 (51)	.66	42 (32)	42 (31)	.90
Medicaid, No. (%)	92 (30)	76 (33)	.55	22 (17)	18 (13)	.44
Wishard Advantage, No. (%)[b]	224 (74)	173 (75)	.87	110 (84)	114 (85)	.80
Other insurance, No. (%)	11 (4)	8 (3)	.91	5 (4)	3 (2)	.45
No insurance, No. (%)	1 (0)	4 (2)	.10	0 (0)	2 (1)	.16
Comorbidities, mean (SD), No.	3.6 (1.3)	3.5 (1.3)	.95	2.4 (1.1)	2.3 (1.1)	.39
All prescription medications, mean (SD), No.	10.4 (4.4)	9.6 (4.0)	.02	6.9 (3.0)	6.8 (3.2)	.82
Cardiovascular medications, mean (SD), No.	2.6 (1.2)	2.6 (1.3)	.55	2.3 (1.1)	2.3 (0.9)	.66
Healthcare system encounters, mean (SD), No.	15 (4)	13 (4)	<.001	2 (1)	1 (1)	<.001

[a] Participants in the complicated strata had a prior diagnosis of heart failure, coronary heart disease, myocardial infarction, stroke, or renal insufficiency, whereas those in the uncomplicated group had hypertension but no evidence of a prior vascular event or complication.
[b] Wishard Advantage is an insurance program available to low-income patients at Wishard Health System.

(n=28), vaginal candidiasis resulting from an orally administered antibiotic (n=14), an increase in serum creatinine level associated with a medication (n=10), inadequate monitoring after prescribing (n=9), and prescription of multiple acetaminophen products (n=7). Most events involved a cardiovascular medication (n=44; 21%) followed by drug interactions involving multiple drug classes (n=39; 18.6%), and then events associated with antimicrobial agents (n=24; 11.4%) or hypoglycemic agents (n=12; 5.7%).

EFFECT OF THE INTERVENTION

Ninety percent of all events occurred in the complicated stratum and 10% in the uncomplicated stratum. For both strata, events were fewer in the intervention groups compared with controls (**Table 3**). In the complicated stratum, 121 events were observed in the control group and 68 in the intervention group. The overall mean (SD) number of events per participant was 0.37 (0.9) for the control group and 0.28 (0.8) for the intervention group

Table 3. Number and Percentage of Events by Complication and Treatment Group Status

Study Group	Events, No. (%)
Complicated Hypertension	
Control	
ADE	75 (35.7)
ADE/ME	22 (10.5)
PADE/ME	24 (11.4)
Subtotal	121 (57.6)
Intervention	
ADE	41 (19.5)
ADE/ME	9 (4.3)
PADE/ME	18 (8.6)
Subtotal	68 (32.4)
Uncomplicated Hypertension	
Control	
ADE	3 (1.4)
ADE/ME	1 (0.5)
PADE/ME	10 (4.8)
Subtotal	14 (6.7)
Intervention	
ADE	4 (1.9)
ADE/ME	1 (0.5)
PADE/ME	2 (1.0)
Subtotal	7 (3.4)
Total	**210 (100)**

Abbreviations: ADE, adverse drug event; ADE/ME, adverse drug event from a medication error (ie, preventable adverse drug event); PADE/ME, potential adverse drug event from a medication error ie, medication error that did not lead to harm.

Table 4. Types and Frequencies of Events

Event Type	Treatment Group, No. (%)	
	Control	Intervention
Renal insufficiency[a]	24 (17.8)	4 (5.3)
Drugs to avoid in the elderly	18 (13.3)	10 (13.3)
Candidiasis	10 (7.4)	6 (8.0)
Monitoring error	8 (5.9)	6 (8.0)
Elevated liver enzyme levels	7 (5.2)	1 (1.3)
Dizziness and/or hypotension	7 (5.2)	4 (5.3)
Toxic drug concentration	6 (4.4)	8 (10.7)
Gastrointestinal adverse event	5 (3.7)	0 (0.0)
Multiple acetaminophens	5 (3.7)	2 (2.7)
Hyperkalemia	4 (3.0)	3 (4.0)
Hypokalemia	4 (3.0)	7 (9.3)
Constipation	4 (3.0)	3 (4.0)
Bleeding, minor	4 (3.0)	2 (2.7)
Bleeding risk	3 (2.2)	3 (4.0)
Allergy	3 (2.2)	6 (8.0)
Hypoglycemia	3 (2.2)	4 (5.3)
Hyperglycemia	3 (2.2)	0 (0.0)
QTc interval change	3 (2.2)	1 (1.3)
Bradycardia	3 (2.2)	0 (0.0)
Heart failure exacerbation	3 (2.2)	0 (0.0)
Diarrhea	2 (1.5)	0 (0.0)
Clostridium difficile colitis	1 (0.7)	2 (2.7)
Miscellaneous[b]	5 (3.7)	3 (4.0)
Totals	**135 (100)**	**75 (100)**

[a] P=.01 by Fisher exact test. No other events showed significant differences.
[b] Miscellaneous category contains events numbering 0 or 1 in control and intervention groups.

(P=.04). In the uncomplicated stratum, there were 14 events in the control group and 7 in the intervention group. The overall mean numbers of ADEs and MEs per participant were 0.07 (0.30) and 0.03 (0.20) for control and intervention groups, respectively (difference not significant). **Table 4** summarizes the types and frequencies of events.

Adverse drug events occurred in 121 participants (15.1%) in the control and intervention groups. Fewer ADEs were observed in the intervention group. In the complicated control group, the mean (SD) number of ADEs per participant was 0.36 (0.9) compared with 0.28 (0.8) in the intervention group (P=.04). While there were also fewer ADEs per participant in the uncomplicated intervention group than in the control group (0.03 [0.20] vs 0.07 [0.30]), the difference was not significant.

Medication errors occurred in 58 participants (7.3%) in the control and intervention groups. There were fewer MEs with the intervention in both the complicated and uncomplicated strata, but the difference was significant only in the uncomplicated stratum: a mean (SD) 0.06 (0.20) MEs per participant were observed in the control and 0.01 (0.10) MEs in the intervention groups (P=.04). In the complicated stratum, there were 0.14 (0.5) MEs per participant in the control group and 0.10 (0.4) in the intervention group (difference not significant).

Risk ratios comparing control and intervention effects by group are listed in **Table 5**. Compared with the control group, the risk of any event was 34% lower in the intervention group (risk ratio, 0.66; 95% confidence interval [CI], 0.50-0.88) including a lower risk of ADEs (risk ratio, 0.65; 95% CI, 0.47-0.90); preventable ADEs (risk ratio, 0.52; 95% CI, 0.25-1.09), potential ADEs (risk ratio, 0.70; 95% CI, 0.40-1.22), and MEs (risk ratio, 0.63; 95% CI, 0.40-0.98). These effects of the intervention were consistent within complicated and uncomplicated strata.

COMMENT

The results of this post hoc analysis suggest that pharmacist intervention to improve medication use in adult outpatients with cardiovascular disease decreases ADEs and MEs. While these findings were the result of a pooled estimate involving 2 studies, the effects were consistent within individual studies. Most of the events (90%) derived from individuals with complicated cardiovascular disease such as heart failure who had more complicated drug regimens.

The focus of the intervention was aimed at improving adherence and medication use by pharmacists spending more of their time instructing patients on the appropriate use of their medications, drug monitoring, and communication with patients' primary care physicians.[14,18] Intervention group participants received (1) careful instruction on how the medications should be used, (2) patient-centered oral and written information, and (3) answers to their medication questions. It is reassuring that the intervention aimed at improving adherence did not increase the risk of ADEs that could occur with increased adherence. However, it is likely that much of the intervention's effect on reducing the risk of

Table 5. Comparison of Intervention and Control Group Medication-Related Events and Errors

Study Group	Risk Ratio (95% Confidence Interval)				
	All Events	ADEs	Preventable ADEs	Potential ADEs	Medication Errors
All participants (N=800)[a]	0.66 (0.50-0.88)	0.65 (0.47-0.90)	0.52 (0.25-1.09)	0.70 (0.40-1.22)	0.63 (0.40-0.98)
Complicated hypertension (n=535)[b]	0.74 (0.55-0.99)	0.68 (0.48-0.95)	0.54 (0.25-1.17)	0.98 (0.53-1.81)	0.77 (0.48-1.24)
Uncomplicated hypertension (n=265)[c]	0.49 (0.20-1.22)	1.23 (0.33-4.58)	0.98 (0.06-15.73)	0.20 (0.04-0.90)	0.27 (0.07-0.96)

Abbreviations: ADEs, adverse drug events; CHF, chronic heart failure.
[a] Participants from both heart failure and hypertension studies.
[b] All heart failure study participants and complicated hypertension participants.
[c] Hypertension participants in the uncomplicated stratum of the hypertension study.

such events in this study derived from pharmacist drug monitoring and communicating with physicians and nurses.

Pharmacists regularly communicated with physicians and nurses concerning patient-reported symptoms, drug-related problems including ADEs and MEs, and changes in important drug-monitoring parameters such as laboratory results affected by drugs. In the 314 patients with heart failure, we previously found that pharmacist intervention improved adherence to cardiovascular medications and patient satisfaction and reduced health care utilization and direct costs of care.[14] While fewer patients experienced ADEs and MEs (37.5% vs 47.4%) (*P*=.09), the study was not statistically powered to reveal the effects of the intervention on patient safety factors. As such, we pooled the data from similarly designed studies involving patients with heart failure and hypertension and observed a decreased risk of adverse events associated with the intervention. The Institute for Safe Medication Practices[28,29] has emphasized the importance of interventions by pharmacists to improve adherence, offer instruction aimed at mitigating deficiencies in health literacy, and enhance communication between health care providers and patients.

Measurement of ADEs and MEs was accomplished using a computer program that had been developed for the purpose of other research.[3,22] The identification of ADEs and MEs using this method underestimates the true incidence of these events for several reasons. First, events were defined a priori based on a list of commonly observed ADEs and MEs in adult outpatients, and as such the universe of events is not represented herein. Also, our inability to assess text data in the hypertension study likely resulted in fewer ADEs manifested by symptoms in that cohort.

Second, methods to identify events using computer programs have generally provided lower estimates than direct observation and survey methods.[4,6] While the negative predictive value of computer-based identification is very good (>80%), positive predictive value is low (<25%).[3,22] Furthermore, we could not determine errors of administration and other events that frequently occur in patients' homes. Nonetheless, we believe that the use of the standardized computer program with blinded expert verification of events adds an important contribution to safety assessment in studies like ours by offering identical event identification protocols for intervention and control groups. Others have suggested that

computer-based surveillance methods may be reasonable for assessing the impact of interventions.[30,31]

Although the severity of harm was not specifically ranked, most of the events were mild; none were life-threatening. The intervention was effective in reducing some but not all harmful events, as illustrated by ACE inhibitor and β-blocker prescribing for patients with heart failure. In the control group, there were more ACE-associated rashes in patients with new prescriptions for these drugs in the intervention group than among controls (intervention, n=4; control, n=1). However, an important part of the intervention in the heart failure study was to remind physicians of the importance of prescribing ACE inhibitors to patients with heart failure. Therefore, it would be expected that prescriptions for these drugs in ACE inhibitor–naïve patients would lead to a greater risk of allergies. In contrast, while prescribing β-blockers for patients with heart failure was appropriately encouraged by pharmacists, fewer patients experienced β-blocker–associated bradycardia (pulse, <60 beats/min) in the intervention group, presumably owing to heightened vigilance by pharmacists who regularly monitored patients' pulses (intervention, n=0; control, n=3). Evidence of bleeding associated with nonsteroidal anti-inflammatory drugs including aspirin can be especially concerning and occurred in 5 and 2 patients in the control and intervention groups, respectively; however, none of these events was severe.

Another potential limitation of the study is that we analyzed 12 months of data for both heart failure and hypertension studies, but the intervention ran only 9 months for the heart failure study. Our reasoning was that there would be future benefits of pharmacist activities to improve the quality and safety of medication use. For example, some nonurgent recommendations made by e-mail or paper notation would be executed by the physician at the patient's next visit, resulting in a delayed benefit. This assumption might not be accurate. In our previous study of pharmacist effects on adherence in these patients, when the intervention stopped, the effects dissipated.[14] However, the adherence effects were largely believed to be the result of direct pharmacist interaction with the patient, while the effects on ADEs and MEs were primarily due to interactions with physicians and nurses.

It is possible that interventions such as ours could have favorable effects on the costs of care. Our economic analysis indicates lower actual direct health care costs associated with the overall effects of the multifaceted interven-

tion compared with those of usual care (–$2676 per patient [95% CI, –$578 to –$5166]). In this same health care setting, Burton et al[32] recently determined that the mean charge for an ADE was $926 in 2006 dollars. Notwithstanding a number of important assumptions, we offer a crude estimate of savings deriving specifically from the intervention's effects on ADEs and MEs. If ADEs amenable to intervention occur in 5% of adult outpatients each year, and the effects of our intervention are generalizable to other disorders in outpatients, then the 35% lower risk of ADEs (observed in this study) in a 50 000-patient outpatient practice could result in a reduction in annual charges to payers of approximately $631 000. We hope that investigators of future studies of pharmacist interventions will more precisely determine such costs. In conclusion, this post hoc analysis of a pharmacist intervention to improve medication use in adult outpatients suggests a lower risk of adverse drug events and medication errors. Further studies are needed to confirm this finding.

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REFERENCES

1. Johnson JA, Bootman JL. Drug-related morbidity and mortality: a cost-of-illness model. *Arch Intern Med.* 1995;155(18):1949-1956.
2. Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash).* 2001;41(2):192-199.
3. Honigman B, Lee J, Rothschild J, et al. Using computerized data to identify adverse drug events in outpatients. *J Am Med Inform Assoc.* 2001;8(3):254-266.
4. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med.* 2003;348(16):1556-1564.
5. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA.* 2003;289 (9):1107-1116.
6. Aspden P, Wolcott JW, Bootman JL, Cronenwett LR. *Preventing Medical Errors.* Washington, DC: National Academies Press; 2006.
7. Shaughnessy AF, Nickel RO. Prescription-writing patterns and errors in a family medicine residency program. *J Fam Pract.* 1989;29(3):290-295.
8. Rupp MT, DeYoung M, Schondelmeyer SW. Prescribing problems and pharmacist interventions in community practice. *Med Care.* 1992;30(10):926-940.
9. Flynn EA, Barker KN, Gibson JT, Pearson RE, Berger BA, Smith LA. Impact of interruptions and distractions on dispensing errors in an ambulatory care pharmacy. *Am J Health Syst Pharm.* 1999;56(13):1319-1325.
10. Thomsen LA, Winterstein AG, Sondergaard B, Haugbolle LS, Melander A. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. *Ann Pharmacother.* 2007;41(9):1411-1426.
11. Field TS, Gilman BH, Subramanian S, Fuller JC, Bates DW, Gurwitz JH. The costs associated with adverse drug events among older adults in ambulatory setting. *Med Care.* 2005;43(12):1171-1176.
12. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc.* 2004;52(8):1349-1354.
13. Hanlon JT, Weinberger M, Samsa GP, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. *Am J Med.* 1996;100(4):428-437.
14. Murray MD, Young J, Hoke S, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Ann Intern Med.* 2007; 146(10):714-725.
15. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA.* 1999;282(3):267-270.
16. Schnipper JL, Kirwin JL, Cotugno MC, et al. Role of pharmacist counseling in preventing adverse drug events after hospitalization. *Arch Intern Med.* 2006; 166(5):565-571.
17. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med.* 2006;166(9):955-964.
18. Murray MD, Young JM, Morrow DG, et al. Methodology of an ongoing, randomized, controlled trial to improve drug use for elderly patients with chronic heart failure. *Am J Geriatr Pharmacother.* 2004;2(1):53-65.
19. Morris AB, Li J, Kroenke K, Bruner-England TE, Young JM, Murray MD. Factors associated with drug adherence and blood pressure control in patients with hypertension. *Pharmacotherapy.* 2006;26(4):483-492.
20. McDonald CJ, Overhage JM, Tierney WM, et al. The Regenstrief Medical Record System: a quarter century experience. *Int J Med Inform.* 1999;54(3):225-253.
21. Murray MD, Smith FE, Fox J, et al. Structure, functions, and activities of a research support informatics section. *J Am Med Inform Assoc.* 2003;10(4):389-398.
22. Seger A, Gandhi T, Hope C, et al. Development of a computerized adverse drug event (ADE) monitor in the outpatient setting. http://www.ahrq.gov/downloads /pub/advances/vol2/Seger.pdf. Accessed December 4, 2008.
23. Hope C, Overhage JM, Seger A, et al. A tiered approach is more cost effective than traditional pharmacist-based review for classifying computer-detected signals as adverse drug events. *J Biomed Inform.* 2003;36(1-2):92-98.
24. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. *J Gen Intern Med.* 1995; 10(4):199-205.
25. Poon EG, Cina JL, Churchill W, et al. Medication dispensing errors and potential adverse drug events before and after implementing bar code technology in the pharmacy. *Ann Intern Med.* 2006;145(6):426-434.
26. Miller DK, Malmstrom TK, Joshi S, Andresen EM, Morley JE, Wolinsky FD. Clinically relevant levels of depressive symptoms in community-dwelling middle-aged African Americans. *J Am Geriatr Soc.* 2004;52(5):741-748.
27. Kroenke K, Wyrwich KW, Tierney WM, Babu AN, Wolinsky FD. Physician-estimated disease severity in patients with chronic heart or lung disease: a cross-sectional analysis. *Health Qual Life Outcomes.* 2006;4:60.
28. Grissinger MC, Globus NJ, Fricker MP Jr. The role of managed care pharmacy in reducing medication errors. *J Manag Care Pharm.* 2003;9(1):62-65.
29. Institute for Safe Medication Practices. A call to action: protecting U.S. citizens from inappropriate medication use. http://www.ismp.org/pressroom/viewpoints /CommunityPharmacy.pdf. Accessed December 4, 2008.
30. Thomas EJ, Petersen LA. Measuring errors and adverse events in health care. *J Gen Intern Med.* 2003;18(1):61-67.
31. Bates DW, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Detecting adverse events using information technology. *J Am Med Inform Assoc.* 2003; 10(2):115-128.
32. Burton MM, Hope C, Murray MD, Hui S, Overhage JM. The cost of adverse drug events in ambulatory care. *AMIA Annu Symp Proc.* October 11, 2007:90-93.